Summary of Safety and Probable Benefit

I. General Information

Device Generic Name:	Pulmonary Valved Conduit
Device Trade Name:	CONTEGRA® Pulmonary Valved Conduit
Applicant's Name and Address:	Medtronic, Inc. 1851 E. Deere Avenue Santa Ana, CA 92705
Humanitarian Device Exemption (HDE) Number:	H020003
Date of Humanitarian Use Device Designation:	April 24, 2002
Date of Panel Recommendation:	None
Date of GMP Inspection:	NA
Date of Notice of Approval:	NOV 21 2003

II. Indications for Use

The CONTEGRA® Pulmonary Valved Conduit is indicated for correction or reconstruction of the Right Ventricular Outflow Tract (RVOT) in patients aged less than 18 years with any of the following congenital heart malformations:

- Pulmonary Stenosis
- Tetralogy of Fallot
- Truncus Arteriosus
- Transposition with Ventricular Septal Defect (VSD)
- Pulmonary Atresia

In addition, the conduit is indicated for the replacement of previously implanted, but dysfunctional, pulmonary homografts or valved conduits.

III. Contraindications

None

IV. Warnings and Precautions

Warnings

FOR SINGLE USE ONLY.
DO NOT RESTERILIZE THE CONDUIT BY ANY METHOD. Exposure of the conduit and its container to irradiation, steam, ethylene oxide, or other chemical sterilants will render the conduit unfit for use.
DO NOT use the conduit under the following conditions:

- the conduit has been dropped, damaged, or mishandled in any way
- the "Use By" date has elapsed
- the seal is broken
- the serial number tag does not match the container label
- the conduit has been exposed to freezing or to prolonged heat (Check freeze indicator. If exposed to a freeze-thaw condition, the indicator vial will break causing the dye to escape and stain the paper backing.)
- the storage solution does not completely cover the conduit

DO NOT expose the conduit to solutions other than the storage and rinsing solutions.
DO NOT allow the conduit to dry. Maintain conduit moisture with irrigation or immersion during surgery.
DO NOT attempt to repair a damaged conduit.
DO NOT use cutting needles, as they may cause structural damage to the conduit.
DO NOT pass a catheter through the conduit, as this may damage the conduit.

Precautions

CAUTION: Exposure to glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure or breathing of the chemical vapor. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water (minimum of 15 minutes). In the event of eye contact, flush with water for a minimum of 15 minutes and seek medical attention immediately.

Specific Patient Populations
The safety and probable benefit of the Contegra® Pulmonary Valved Conduit has not been established for the following specific populations because it has not been studied in these populations:

Patients who are pregnant;
Nursing mothers;

Patients with abnormal calcium metabolism (e.g., chronic renal failure, hyperparathyroidism)
Patients with aneurysmal aortic degenerative conditions (e.g., cystic medial necrosis, Marfan's Syndrome)

In addition, the clinical data provided to support the safety and probable benefit of the Contegra® Pulmonary Valved Conduit were limited in some areas (see section X. Summary of Clinical Information).

Patient Counseling
In some conditions, patients may require anticoagulation and/or antiplatelet therapy for an indefinite period.

Patients with bioprostheses are at risk for bacteremia (e.g., undergoing dental procedures) and should be advised about prophylactic antibiotic therapy.

V. Device Description

The device is a glutaraldehyde-crosslinked, heterologous bovine jugular vein with a competent tri-leaflet venous valve and a natural sinus slightly larger in diameter within its lumen than the diameter of the adjacent conduit.

The device is available in even increments between 12 and 22 mm inside diameter, measured at the inflow end. The overall length of the device is about 10cm, except for the 12mm models, which are approximately 7cm in length. The valve and valve sinus are located at approximately the middle of the device.

The device is available in two models: one without external ring support (Model 200), and the other with ring support modification (Model 200S). The latter consists of an attachment of two polyester-knit-cloth covered polypropylene rings sutured to the adventitial layer of the device (with polytetrafluoroethylene suture). One ring is attached at the level of the commissures, and the other is attached at the level of the annulus of the valve leaflets.

VI. Alternative Practices and Procedures

Alternatives available for correction of the cardiac anomalies of the RVOT include implantation of homografts, non-valved conduits, shunts, or bioprostheses consisting of woven Dacron tubes as supportive housing for mechanical, glutaraldehyde-fixed porcine, or bovine pericardial valves. The Shelhigh Pulmonic Valve Conduit is indicated for similar uses and was approved via the Humanitarian Use Device Exemption on September 30, 1999. A description of the comparisons of safety and probable benefit with the

11

available alternative devices is provided in Section XI, Risk Probable Benefit Analysis.

VII. Marketing History

The device has been marketed in the United Kingdom, Spain, the Netherlands, Belgium, Norway, Denmark, Finland, Germany, Austria, Switzerland, France, Italy, and Greece. The Contegra® Pulmonary Valved Conduit has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. Potential Adverse Events

Observed adverse events:

Contegra® Pulmonary Valved Conduit Clinical Study

The following clinical data are interim data from an ongoing clinical investigation of the Contegra® Pulmonary Valved Conduit.

A prospective, non-randomized, multi-center evaluation is being conducted of patients implanted with the Contegra® Pulmonary Valved Conduit. The following data were obtained from 237 patients implanted at sixteen centers. Cumulative follow-up for these 237 patients was 307.7 patient-years with a median follow-up of 1.0 year (range 0 years to 3.5 years). Adverse events, including death, were captured throughout the postoperative period and are summarized in the tables below.

Table 1. Mortality Rates Following Implant with the Contegra® Pulmonary Valved Conduit

European Companion Study and US Study (N=237)	Early Events[1] n (% of patients)	Late Events[2] n (%/patient-year)[3]	Freedom From[4] Death at 1 Year (SE)	Freedom From[4] Death at 2 Years (SE)
All Death	22 (9.3%)	6 (2.1%)	88.1% (2.7%)	87.3% (3.9%)
Non Device-Related[5]	18 (7.6%)	0 (0.0%)	92.1% (2.3%)	92.1% (3.3%)
Device-Related or Unexplained	4 (1.7%)	6 (2.1%)	95.6% (1.8%)	94.8% (2.7%)
Device-Related	2 (0.8%)	5 (1.8%)	97.0% (1.5%)	96.2% (2.4%)
Unexplained	2 (0.8%)	1 (0.4%)	98.6% (1.1%)	98.6% (1.5%)

Notes:

1. ≤30 days postoperative if the patient was discharged from the hospital, or at any time after implant if the patient was not discharged from the hospital
2. Greater than 30 days postoperative if the patient was discharged from the hospital
3. Calculations were based on 284.0 late patient-years.
4. Kaplan-Meier method was used to estimate survival and Peto's formula was used for the calculation of the standard errors of these estimates.
5. Twelve early deaths were cardiac and six early deaths were noncardiac.

Table 2. Morbidity Rates Following Implant with the Contegra® Pulmonary Valved Conduit

European Companion Study and US Study (N=237)	Early Events[1] n (% of patients)	Late Events[2] n %/patient-year[3]	Freedom From[4] Event at 1 Year (SE)	Freedom From[4] Event at 2 Years (SE)
Endocarditis	1 (0.4%)	2 (0.7%)	98.6% (1.0%)	98.6% (1.5%)
Thrombus[5]	5 (2.1%)	6 (2.1%)	95.4% (1.8%)	93.7% (3.0%)
Reoperation[6,7]	3 (0.8%)	22 (7.6%)	92.4% (2.3%)	86.1% (4.1%)
Explant	1 (0.4%)	11 (3.8%)	97.6% (1.4%)	92.0% (3.3%)
Minor Hemorrhage[8]	12 (4.2%)	2 (0.7%)	94.4% (2.0%)	94.4% (2.9%)
Major Hemorrhage[9]	31 (10.5%)	4 (1.4%)	88.0% (2.9%)	88.0% (4.1%)
Catheter Intervention[7,10]	2 (0.4%)	39 (13.5%)	86.8% (3.0%)	80.2% (4.7%)

Notes:
1. ≤30 days postoperative
2. Greater than 30 days postoperative
3. Calculations were based on 289.7 late patient-years.
4. Kaplan-Meier method was used to estimate survival and Peto's formula was used for the calculation of the standard errors of these estimates.
5. There were four (4) additional cases of focal thrombus deposition on the valve surface, on the conduit, or at the pulmonary artery anastomosis of the conduit which were considered by the core lab pathologist to be of insufficient amount to be primary valve thrombosis or to interfere with valve function.
6. Reoperation includes explant and surgical repair involving the Contegra device.
7. One patient had two early events.
8. Two patients had two early events.
9. Three patients had two early events and one patient had four early events.
10. Catheter intervention includes balloon dilation or stent placement in the branch PA, PA bifurcation, and/or distal anastamosis.

Potential Adverse Events:

Prosthetic heart valves have been associated with serious complications, sometimes leading to reoperation and/or death. In addition, complications caused by immunogenic response to the conduit or to physical, chemical, or biological changes, may occur at undetermined intervals, and may require reoperation and replacement of the conduit. As this conduit is indicated for patients aged less than 18 years, reoperation and replacement of the Contegra® Pulmonary Valved Conduit may be indicated because of the patient's physical growth.

General complications reported with valved conduits and biological tissue valves implanted in the heart include the following:
Endocarditis
Hemolysis
Hemorrhage (including anticoagulant-related hemorrhage)
Immunologic rejection
Prosthesis calcification (intrinsic and extrinsic)
Prosthesis (conduit) dilatation
Prosthesis nonstructural dysfunction (e.g., neointimal thickening and peeling)
Prosthesis regurgitation

Prosthesis structural deterioration (perforation, thickening, myxomatous degeneration)
Prosthesis stenosis
Prosthesis thrombosis
Pulmonary hypertension
Thromboembolism

It is possible that these complications could lead to:
Reoperation
Explantation
Permanent disability
Death

These complications may present clinically with abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrhythmia, hemorrhage, low cardiac output, pulmonary edema, myocardial infarction, hemolytic anemia, and congestive heart failure.

IX. Summary of Preclinical Studies

The following summarizes the *in vitro* preclinical testing performed: pulsatile forward flow, pulsatile back flow, steady forward flow, steady back flow, accelerated wear testing, and Bernoulli relation. The following table summarizes the *in vivo* preclinical testing performed.

In vivo Testing

Test Performed	# Test/ Control Animals, Implant Duration	# Test/ Control Samples	Study Objectives	Results
Extracardiac placement in dogs	19 mongrel dogs (18-24kg) 5 months No controls used	12, 14, 16, 18mm sizes used	•to determine long term function using survival, angiography and hemodynamic parameters •to determine the host response to device •to determine potential for thrombosis/embolism •to compare the effects of complete vs. partial occlusion of the native pulmonary tract on the implanted device	The study objectives were met. The devices continued to be functional when measured by hemodynamic parameters. The host responses were consistent with those reported for other glutaraldehyde-fixed heterografts, and within the range of acceptable biocompatibility results. The valve leaflets were not affected by host response including mineralization and appeared to function in the presence of fibrin thrombi. Fibrous intimal peel was not present in any of the test articles.
Pulmonary position placement in sheep	9 juvenile sheep controls: 3 sheep implanted with the Medtronic Hancock conduit	20mm unsupported	•to establish long-term (>5 month) function of the device using survival and ECHO evaluations •to examine the host response to the device •to compare the results with a composite conduit (Medtronic Hancock conduit)	The study objectives were met. Calcification of test articles was less than the control devices. The test articles were completely functional, and the control devices showed questionable function. The test articles had overall better results in the degree of host response as fibrous sheath ingrowth. Both gross and histopathologic evaluations

				showed appreciably greater growth in the control devices than in the test articles.

X. Summary of Clinical Information

Contegra® Pulmonary Valved Conduit Clinical Study

The following clinical data are interim data from an ongoing clinical investigation of the Contegra® Pulmonary Valved Conduit.

A prospective, non-randomized, multi-center evaluation is being conducted of patients implanted with the Contegra® Pulmonary Valved Conduit. The following data were obtained from 237 patients implanted at sixteen centers. Cumulative follow-up for these 237 patients was 307.7 patient-years, with a median follow-up of 1.0 year (range 0 years to 3.5 years). Preoperative data, safety, effectiveness, and comparative literature data are presented in the tables below.

Table 3. Preoperative Data (N=237)

Variable	Category	n	%
Age at Implant	Less than 3 months	46	19.4
	3 to 12 months	37	15.6
	13 to 24 months	44	18.6
	25 months to 5 years	48	20.3
	6 to 10 years	33	13.9
	Greater than 10 years	29	12.2
Gender	Male	138	58.2
	Female	99	41.8
Primary Indication for Surgery	Replacement of Previous Conduit	77	32.5
	Tetralogy of Fallot	62	26.2
	Truncus Arteriosus	38	16.0
	Aortic Valve Disease	21	8.9
	Double Outlet	15	6.3
	Pulmonary Atresia	13	5.5
	Transposition of Great Arteries	8	3.4
	Pulmonary Stenosis	3	1.3

Table 4. Risk Factors Associated with Time to Death (All Causes) (n=237)

Risk Factor	Relative Risk	95% Confidence Interval	P-Value
Age at Implant			
Less Than 3 Months	4.81	1.99 - 11.61	0.0005
Concomitant Procedure			
Mitral/Tricuspid Valve Repair	20.42	5.96 – 70.44	< 0.0001
Aortic Valve/Root Replacement	8.62	2.60 – 28.38	0.0004
Ventricular Septum Repair	4.56	1.50 – 13.97	0.0082

Cox Proportional Hazards Survival regression analysis was used to assess the association of risk factors and time to event.

Table 5. Risk Factors Associated with Time to Reoperation (n=237)

Risk Factor	Relative Risk	95% Confidence Interval	P-Value

Age at Implant			
Less Than 24 Months	4.11	1.39 – 12.04	0.0105

Cox Proportional Hazards Survival regression analysis was used to assess the association of risk factors and time to event.

Table 6. Risk Factors Associated with Time to Explant (n=237)

Risk Factor	Relative Risk	95% Confidence Interval	P-Value
Primary Indication for Surgery			
Tetralogy of Fallot	16.05	1.92 – 132.53	0.0102
Truncus Arteriosus	12.44	1.38 – 111.63	0.0246

Cox Proportional Hazards Survival regression analysis was used to assess the association of risk factors and time to event.

Table 7. Comparative Literature (Homograft vs. Contegra® Pulmonary Valved Conduit)

Author/yr	# pts	Mean age (SD or range) d=day m=month y=year	Death (%)		Freedom From reop @1yr[4] (%)	Catheter intervention- % of pts having a cath interv. (%)	Regurgitation	
			Early	Freedom From @1yr			# pts eval.	≥ mod regurg (%)
Medtronic, Contegra 2003	237	2.0 y[1] (1d-19y)	9	88	92	12.2	95[2]	21[2]
Albert, 1993	139	3.0 y (6d-17y)	17	83[3]	98[3]			
Baskett, 1996	44	6.2y (3d-20y)	7	93[3]	95[3]		38	29
Bielefield, 2001	223	2.8y (5d-17y)	14	84[3]	97[3]			
Chan, 1994	41	3.1y[1](3m-28y)				9.8	43	35
Dittrich, 2001	23	1.9y (5d-9y)	13	--	93	4.3	20	15
LeBlanc, 1998	76	3.1y (6d-19y)	5	93	96			
Perron, 1999	84	26d (1d-3m)	11	81	91	20.2		
Schorn, 1997	63	1.3y (±0.9y)	27	--	92	12.7		
Stark, 1998	405	6.8y (--)			97[3]	3.2		
Tam, 1995	56	3.6y[1](1d-24y)	16	84[3]	100		39	36
Tweddell, 2000	205	6.9y (3d-48y)	11	89[3]	95			

[1]median
[2]at one year
[3]estimated from graph in article
[4]For Homograft references: Freedom from reoperation is explant; for Medtronic, Freedom from reoperation includes explant and surgical repair.
shaded cells: no data available

Literature-Based Controls:

Selection Criteria: Homograft clinical studies published since 1993, where the mean patient age at implant was less than seven years were used as comparative literature for death, reoperation, and morbidity. Due to the limited comparative literature for morbidity, clinical studies reporting morbidity in which mean age at implant was seven years or older were also used. Regurgitation references were chosen on the basis that similar methods were cited for assessing the severity of regurgitation. Furthermore,

the studies of Chan (1994) and Baskett (1996) employed the same regurgitation criteria used in the Contegra® study.

References	Place of study Dates of enrollment N (number of patients) Mean age at implant (SD or range)	Data obtained from the source
Albert JD, Bishop DA, Fullerton DA, et al. Conduit reconstruction of the right ventricular outflow tract: lessons learned in a 12-year experience. J Thorac Cardiovasc Surg 1993; 106:228-235.	Denver, CO Sep 1979 – Jul 1991 N – 139 Age – 3.0y (6d-17y)	Mortality, morbidity, reoperation
Baskett RJ, Ross DB, Nanton MA, Murphy DA. Factors in the early failure of cryopreserved homograft pulmonary valves in children: preserved immunogenicity? J Thorac Cardiovasc Surg 1996; 112:1170-1179.	Halifax, NS Dec 1990 – May 1995 N – 44 Age – 6.2y (3d-20y)	Mortality, regurgitation, morbidity, reoperation
Bielefeld MR, Bishop DA, Campbell DN, et al. Reoperative homograft right ventricular tract reconstruction. Ann Thorac Surg 2001; 71:482-488.	Denver, CO Feb 1985 – Mar 1999 N – 223 Age – 2.8y (5d-17y)	Mortality, morbidity, reoperation
Chan KC, Fyfe DA, McKay CA, et al. Right ventricular outflow reconstruction with cryopreserved homografts in pediatric patients: intermediate-term follow-up with serial echocardiographic assessment. J Am Coll Cardiol 1994; 24:483-489.	Charleston, SC Dec 1986 – Oct 1992 N – 41 Age – 3.1y[m] (3m-28y)	Morbidity, regurgitation
Dittrich S, Alexi-Meskishvili VV, Yankah AC, et al. Comparison of porcine xenografts and homografts for pulmonary valve replacement in children. Ann Thorac Surg 2000; 70:717-722.	Berlin, Germany Jan 1994 – Oct 1997 N – 23 Age – 1.9y (5d-9y)	Mortality, regurgitation, morbidity, reoperation
LeBlanc JG, Russell JL, Sett, SS, Potts JE. Intermediate follow-up of right ventricular outflow tract reconstruction with allograft conduits. Ann Thorac Surg 1998; 66:S174-178.	Vancouver, BC Jun 1984 – Aug 1996 N – 76 Age – 3.1y (6d–19y)	Mortality, morbidity, reoperation
Perron J, Moran AM, Gauvreau K, et al. Valved homograft conduit repair of the right heart in early infancy. Ann Thorac Surg 1999; 68:542-548.	Boston, MA 1990 – 1995 N – 84 Age – 26d (1d-3m)	Mortality, morbidity, reoperation
Schorn K, Yankah AC, Alexi-Meskhishvili, et al. Risk factors for early degeneration of allografts in pulmonary circulation. Eur J Cardiothorac Surg 1997; 11:62-69.	Berlin, Germany. Jan 1988 – Mar 1995 N – 63 Age – 1.3y (±0.9y)	Mortality, morbidity, reoperation
Stark J, Bull C, Stajevic M, et al. Fate of subpulmonary homograft conduits: determinants of late homograft failure. J Thorac Cardiovasc Surg 1998; 115:506-516.	London, UK 1971 – 1993 N – 405 Age – 6.8y (–)	Morbidity, reoperation
Tam RK, Tolan MJ, Zamvar VY, et al. Use of larger sized aortic homograft conduits in right ventricular outflow tract reconstruction. J Heart Valv Dis 1995; 4:660-664.	South Hampton, UK Jul 1973 – Jul 1993 N – 56 Age – 3.6y[m] (1d-24y)	Mortality, regurgitation, reoperation
Tweddell JS, Pelech AN, Frommelt PC, et al. Factors affecting longevity of homograft valves used in right ventricular outflow tract reconstruction for congenital heart disease. Circulation 2000; 102(Suppl 3):III-130-135.	Milwaukee, WI Nov 1985 – Apr 1999 N – 205 Age – 6.9y (3d-48y)	Mortality, morbidity, reoperation

[m] median; y - years; m - months; d - days

Since literature data could not be found, note that the morbidity rates of the Contegra® Pulmonary Valved Conduit could not be compared with those of the control for the following complications: hemolysis and thrombosis.

The effectiveness parameters that were collected included peak gradient, mean gradient, and regurgitation data. The data were sufficient to provide reasonable assurances of the probable benefit of the Contegra® Pulmonary Valved Conduit.

The clinical experience, to date, was limited in the following areas:

- Patients above the age of 4 years accounted for only approximately 30% of the total patient population.
- The primary indication for surgery was dominated by, "replacement of previously implanted but dysfunctional pulmonary homografts or valved

conduits", "Tetralogy of Fallot", and "Truncus Arteriosus"; the other indications accounted for only approximately 26% of the intended indications.

- The use of the Model 200S was limited to only approximately 14.3% of the total implants.
- Orthotopic placement was limited to only approximately 24.1% of the total implants.

XI. Risk/Probable Benefit Analysis

The *in vitro* testing consisted of hydrodynamic and accelerated wear testing, and were designed to provide information about the function of the device in controlled *in vitro* conditions. The results suggest that the Contegra® Pulmonary Valved Conduit should perform as anticipated when implanted in human patients.

The *in vivo* animal testing were chronic implant studies using dogs as a model for extracardiac implantation, and sheep for orthotopic implantation. Both studies evaluated safety and function and met their respective study objectives.

The clinical data summarize preoperative, operative, hemodynamic, and safety data from 237 patients implanted with the Contegra® Pulmonary Valved Conduit. To date, the device performs as expected with regard to hemodynamic performance and the incidence of conduit-related adverse events. Although the data are interim and do not demonstrate effectiveness, we believe the data are sufficient to support a determination of probable benefit.

It is expected that the device will undergo replacement due to pediatric patient growth. It is an interim device that provides the physician with a tool to manage the patient until the patient attains growth to allow consideration of other alternatives for their congenital cardiac repair.

The current device alternatives available include patches, valveless conduits, composite prosthetic conduits (mechanical and tissue derived) and human homografts. Since the homograft is currently the most preferred repair device and offers more literature information, Medtronic has chosen to use homograft literature to evaluate the device as an alternative device.

Portions of an extensive literature review are contained in Table 7 of this document. Table 7 summarizes the relevant morbidities of the Contegra® Pulmonary Valved Conduit compared with the literature regarding the use of homografts.

The benefits unique to this device include the off-the-shelf availability of small sizes, as compared with homografts, the natural continuity between the valve and conduit, and the ability to use the device without the need for proximal or distal extension.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available or alternative forms of treatment when used as indicated in accordance with the directions for use.

XII. Panel Recommendation

This HDE was not referred to the Circulatory Systems Device Panel for review and recommendation because the information in the HDE substantially duplicates information previously reviewed by this panel.

XIII. CDRH Recommendation/Decision

CDRH has determined that, based on the data submitted in the HDE, that the Contegra® Pulmonary Valved Conduit will not expose patients to an unreasonable or significant risk or illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury, and issued an approval order on November 21, 2003.

XIV. Approval Specifications

Instructions for Use
Patient Brochure

XV. References

See Section X